QbD Pilot Experience

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The Project

- **CHANTIX™**
  - **Varenicline tartrate for smoking cesation**
  - **Priority Review**
  - **Approved May 10th**
  - **Tablet formulation**
  - **Two strengths**

Selection Criteria

- Available submission in the appropriate timeframe for the pilot program
- Classical dosage form
- Classical chemical synthesis
- Significant “QbD” work had occurred during development

History

- CMC EOP2 meeting held in 2004
- Drug Substance
  - Much of the development occurred prior to QbD discussions
  - Well characterized synthesis and molecule
- Drug Product
  - Subject of internal initiative, “Right First Time”
  - Formal risk assessment and design of experiments
  - Consistent with QbD
- Much of the submission was complete before the announcement of the pilot program

The Pilot

- Extensive development information
  - Expanded P2 and S2.6
  - Focused on information
    - Data analysis and summaries
  - Because of what was already complete, primarily used information already available
  - Described “Design Space” for both DS and DP
- Quality Overall Summary
  - Stand alone review document
    - Module 3 not reviewed
  - Drawn heavily from Module 3 because of time constraints
  - Adjusted based on presubmission FDA input
- Regulatory Agreement
  - Discussed prior to submission
  - Built during the review process

Communications

- Good availability of Review Team and Leadership
- Open and frank dialog
- Lack of clarity about purpose/style of some meetings
- Transparency of review progress at times challenging
- Role of Field in the dialog unclear

Review

- Lots of dialog regarding definitions
  - Critical, key, non-critical
- Difficult to review Design Space without understanding what the applicant is going to do with it operationally post-approval
- Internally, we could have explored operational implementation issues more extensively
- These issues raised the prominence of the regulatory agreement during the review process

QOS

- Did serve the purpose of the review document
  - Did not reach back to module 3
- Still great opportunity to assess how it was used during the review and optimize for reviewer efficiency
- Must assess how it will be kept current

Development Information

- **Allowed a productive dialog on many manufacturing process topics**
  - **In a few cases, triggered more inquiries with questionable regulatory relevance**
- **When an area of concern was identified in the development information (impurities) the dialog on that topic took on an unwarranted prominence possibly because of the extensive development work included to describe the controls. Extensive queries.**
- **Topics of current interest (e.g. blend uniformity) still generated extensive queries and dialog even with comprehensive development analyses provided**

Regulatory Agreement

- Became much more important as the review progressed
- Challenge to assess its meaning internally for the applicant as well as in the review process
- Key to understanding design space because one has to understand what you are going to do with it
- Focus to date has been on manufacturing processes and design space
  - Still great opportunities to assess how to use for other post-approval issues
- Unclear how FDA Field will participate and utilize (e.g. No PAI)
- Discussions with Agency continuing

Miscellaneous Observations

- **Despite best efforts, many issues are still resolved at the end of the review**
- **With all of the focus on QbD, classical regulatory issues still must be dealt with, and arise at the last moment**
  - **e.g. Nomenclature and labeling**
- **Integration of the Field still not transparent**

Summary

- Technical and development information did allow that dialog to focus on science of the product rather than the adherence to arbitrary guidelines
- More dialog regarding the operational use of all of this information in the manufacturing environment will help clarify its development and use in the assessment process
- Change is a hard process, at times not as fast as we would like and we must be realistic with expectations
  - This holds for the applicant as well as for the FDA
- Trust Intent
  - While at times some of the dialog was challenging, the intent behind the review, both for the patient and the new assessment process was honest and pointing in the right direction